

HH 39 R2

April 23, 1941.

Dr. A. D. Hershey  
Department of Bacteriology  
Washington University, School of Medicine  
St. Louis, Mo.

Dear Doctor Hershey:

Under separate cover I am returning your 'phage calculations and sending a set of our Immunochemistry Conference preprints containing Dr. Kendall's calculations.

With regard to the 'phage MS I am afraid I am not well enough acquainted with the intimacies of the reaction to judge whether or not the application of your method of analysis is justified. However, I am quite sure that I do not agree entirely with your conclusions, especially insofar as these are based on your pneumococcus calculations.

To go back to these: while Dr. Morris certainly established her point, her measurements would seem to me inapplicable to any rigid kinetic study of the Pn-anti-Pn reaction. In the first place the Pn and antibody had to be mixed, and it was not until after this was done (and probably most of the reaction was over) that mixtures were chilled and allowed to stand quietly. Even at 0°, how will you evaluate the portion of the reaction taking place during mixing and the portion taking place after mixing? From the very crude velocity measurements Kalat and I published some years ago this would easily introduce an error sufficiently large to invalidate any calculations or conclusions. At every measurement and at each dilution you introduce a similar uncertainty, so that whether or not your calculations agree with any formula would carry little weight. They might also differ by  $10^4$  from your 'phage result and still be due to the same mechanism. I think, for the same reason, that you know nothing of the temperature coefficient of the Pn-anti Pn reaction. Therefore, if your conclusion regarding diffusion is the correct one, much better and more rigid evidence is needed to establish it.

In my lack of personal experience with the 'phage system I cannot help feeling that similar considerations apply. My only specific criticisms, however, would be to certain statements on p. 19 of your MS. For instance, if you obtain no evidence by your study of the heterogeneity of pneumococcus anticarbohydrate, that should be another danger sign to you, for heterogeneity of antibody has been amply demonstrated and confirmed in many systems. If anti-'phage is an exception the burden of proof is on you.

Moreover, while carboxyl groups may play a part in Pn type-specificity and condition certain initial ionic interactions, not all Pn type-substances contain appreciable  $-COOH$  and many other equally reactive specific polysaccharides do not. Also, in the presence of 0.9% salt, antigen-antibody Coulomb forces, unless you mean merely ionization, could scarcely play a large part.

I am sorry to have to be so discouraging toward a very sincere and painstaking effort to make progress. You will remember that I said nothing about your paper until you drove me into a corner and forced me to. I have the distinct feeling that even the excellent mathematical treatment you have given both reactions is a distinct danger in its very exactness if the data used do not fall into the same rigorous category. I have attempted to obtain data on the kinetics of immune reactions, but have only published the crude measurements obtained with Kabat and a few slightly less crude measurements with Treffers and Tager in the Ea-horse anti-Ea system, drawing only the conclusion that the main reaction is faster than had been supposed. Nor have I found any convincing data in the literature. The problem is rendered immeasurably more difficult by the established heterogeneity of antibody.

Hoping you do not mind this forthright expression of opinion and trusting that it will encourage you to think up more rigid experiments along the same lines, and with all good wishes,

Sincerely,

MH/m

Michael Heidelberger.